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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/840,704	04/23/2001	Shoukat Dedhar	KINE001CON2	5167

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/840,704	DEDHAR ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *23 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *2,3,11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a response to the Election filed 1/23/03, in Paper No. 12.

Claims 1-18 are pending in the instant application.

Claims 2, 3, 11 and 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

Claims 1, 4, 5-10 and 13-18 have been examined to the extent they read on the elected subject matter.

Election/Restrictions

Applicant's election with traverse of Group III (claims 1, 4, 5-10 and 13-18) in Paper No. 12 is acknowledged. The traversal is on the ground(s) that all of the claims represent a species of a genus of small organic molecules as inhibitors of integrin linked kinase. Further, Applicant argues that each of the claimed small organic molecule inhibitors of integrin linked kinase share a common function, namely blocking the activity of integrin linked kinase. This is not found persuasive because, as argued in the restriction requirement (Paper No. 9), although the small organic molecule inhibitors of integrin linked kinase share a common function, the different inventions have different modes of operation and are distinct because they are drawn to methods using different materials having different chemical structures, different physical properties and different biological functions. For example, the integrin linked kinase antisense of Group I binds to nucleic acids and the integrin linked kinase antibody of Group II binds to proteins. Furthermore, a search for the antibody of Group II will not encompass all of the art relevant to

the small organic molecule of Group III. The differences between Inventions I, II and III are further underscored by their different classifications and independent search status. Therefore, they are patentably distinct from each other.

The requirement is still deemed proper and is therefore made FINAL.

Priority

The reference to priority in the first line of the Specification should be updated with current serial numbers where patents have issued. Appropriate correction is required.

Applicant's claim for domestic priority under 35 U.S.C. 120 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 5-10 and 13-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "integrin-linked kinase" in claims 1, 5, 10 and 14 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what would be considered an "integrin-linked kinase". It is unclear whether the kinase in linked covalently to the integrin or the kinase is associated with the activity of the integrin.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 5-10 and 13-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1, 4, 5-10 and 13-18 are drawn to a method of inhibiting or preventing inflammation in a host, comprising contacting said host with an inhibitor of integrin linked kinase.

Given their broadest reasonable interpretation, the claims encompass inhibiting or preventing inflammation (*in vivo)* using inhibitors of integrin linked kinase, including small organic molecules, wortmannin and LY294002.

The instant specification as filed describes the assessment of integrin linked kinase activation by insulin on IEC-18 cells (*in vitro*) using wortmannin and LY294002 (see Example 13).

Berrie, CP (Expert Opinion in Investigational Drugs, 2001 Vol. 10:1085-1098) assert that while wortmannin has been classified as a 'standard' inhibitor of phosphoinositide 3-kinase, an integrin linked kinase, it is also an inhibitor of phospholipase D (PLD), phospholipase C (PLD), phospholipase A2 (PLA_2), myosin light chain kinase and pleckstrin phosphorylation. Berrie, CP also assert that LY294002, also a 'standard' inhibitor of phosphoinositide 3-kinase like

wortmannin, has non-specific inhibitory effects on casein kinase 2, a key factor in many regulatory processes. Berrie, CP also assert that despite their experimental use in parallel for confirmation of effects, further specificity of action is needed by wortmannin and LY294002 (see page 1089, first and second columns). Berrie, CP further assert that the search for effective non-toxic drugs for use in treatment needs to be further correlated with the specific *in vivo* effects on cell survival, invasivity and metastatic potential (see Abstract).

Stein, RC (Endocrine-Related Cancer, 2001 Vol. 8:237-248) assert that the lack of selectivity among wortmannin and LY294002, together with the instability of wortmannin and the insolubility of LY294002, means that neither has very promising pharmaceutical potential (see page 242, second column).

The assertions of Berrie, CP and Stein, RC indicate that due to the non-specific inhibitory effects of wortmannin and LY294002, further research is required in the art to employ other, more specific inhibitors of integrin linked kinase.

In view of the unpredictability in the art, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention without having to engage in trial and error or undue experimentation. The specification as filed contemplates the therapeutic use of integrin linked kinase inhibitors, including small organic molecules, wortmannin and LY294002.

However, the instant specification does not show any specific link between the assessment of integrin linked kinase activation by insulin on IEC-18 cells (*in vitro*) using wortmannin and LY294002 such that inhibiting or preventing inflammation in a host, comprising contacting said host with an inhibitor of integrin linked kinase would be an apparent therapeutic

option. It is unclear how the specific cell culture (*in vitro*) data is correlated with/or representative of inhibiting or preventing inflammation in a host. It is also unclear how integrin linked kinase inhibitors, including small organic molecules, wortmannin and LY294002 will inhibit or prevent inflammation in a host where no specific guidance (i.e. specific mode of treatment, delivery route, tissue specificity, etc.) is provided.

The specification does not provide particular guidance or particular direction for the inhibition or prevention of inflammation in a host. The specification does not provide guidance for the specificity of wortmannin and LY294002 inhibition of integrin linked kinase in a host. While the specification provides guidance to the assessment of integrin linked kinase activation by insulin on IEC-18 cells (*in vitro*) using wortmannin and LY294002, the specification provides no particular nexus between inhibiting or preventing inflammation in a host, *in vivo*, as contemplated by the specification. The specification provides no particular guidance of direction for addressing the problems of specificity, targeting, permanence and quantity of inhibition of wortmannin and LY294002 for targeting an integrin linked kinase in a host, for example. Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art, at the time of the invention, would have required an undue amount of experimentation to make and use the claimed invention. Due to the lack of specific guidance in the specification as filed and the lack of correlation between the assessment of integrin linked kinase activation by insulin on IEC-18 cells (*in vitro*) using wortmannin and LY294002 and inhibiting or preventing inflammation in a host, *in vivo*, one of skill in the art would require specific guidance to practice the current invention. The current specification does not provide such guidance for inhibiting or preventing

inflammation in a host, *in vivo* and one of skill in the art would be required to perform trial and error or undue experimentation. The quantity of experimentation required to practice the invention would include the de novo determination of how to deliver wortmannin and LY294002 targeting integrin linked kinase in a host, *in vivo*, such that inflammation is inhibited or prevented to any degree, particularly, in view of the obstacles needed to overcome to use wortmannin and LY294002 therapies as exemplified in the references discussed above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 5, 6, 7, 10, 13, 14, 15 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Norman et al. (Journal of Medicinal Chemistry, 1996 Vol. 39:1106-1111).

Claims 1, 4, 5, 6, 7, 10, 13, 14, 15 and 16 are drawn to a method of inhibiting or preventing inflammation in a host comprising contacting said host with an inhibitor of integrin linked kinase.

Norman et al. disclose wortmannin was evaluated in in vivo tumor models using daily po dosing to find an appropriate model for antitumor evaluation of wortmannin and related analogs (see Table 2).

Therefore, Norman et al. anticipate the current invention.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
March 19, 2003

Ram R. Shukla
RAM R. SHUKLA, PH.D
PATENT EXAMINER